# ADULT MINIMAL CHANGE NEPHROPATHY: EXPERIENCE OF THE COLLABORATIVE STUDY OF GLOMERULAR DISEASE*

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## INTRODUCTION

Minimal change nephropathy is a name derived from histologic findings and is applied to the type of nephrotic syndrome that occurs commonly in small children, but in adults of all ages as well. The usual presentation is a sudden appearance of edema accompanied by large scale proteinuria consisting predominently of albumin. Hypoalbuminemia, hyperlipidemia and lipiduria accompany the proteinuria.

Blood pressure is usually normal as is the glomerular filtration rate. Patients are susceptible to the occurrence of venous thromboses. Infection including cellulitis and peritonitis mediated by Gram positive organisms such as streptococcus and pneumococcus occurred frequently and were the cause of significant mortality.

## PATHOLOGY

On light microscopy the glomeruli appear normal or may have a very slight increase in mesangial cells and matrix. Immunofluorescence studies characteristically show no deposition of immunoglobulin though small amounts of IgM may be present. Electron photomicrographs show no abnormalities except for a loss of discrete "foot processes" of the epithelial cells surrounding the capillary loops. This isolated abnormality, now known to be associated with a loss of the normally dense negative charges on the capillary wall, gives the condition the name "minimal change."

## TREATMENT

Historically, many approaches to treatment have been explored. In addition to salt restricted and protein enriched diets such seemingly odd therapies as the induction of measles were tried. This last was based on the observation that occasionally diuresis occurred in nephrotic children soon after the natural occurrence of a febrile illness. Mercurial and other diuretics were used as they became available, as were antibiotics for the infections. George Thorn (1) and John Luetscher (2) and their colleagues

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began to use ACTH and cortisol at an early stage of their availability and found occasional dramatic responses (though sometimes this occurred after discontinuing the drug.) With diuretics, antibiotics and steroids the mortality rate from the disease fell substantially, but note that it is difficult or impossible to separate the individual contributions of these three therapies.

Prednisone therapy, in a dose approximating 50 mg/$M^2$/d for a period of 4 weeks leads to a complete remission of proteinuria in some 90% of patients (3). The problem with this therapy is that the majority of patients will subsequently relapse at least once, and many patients will require either frequently repeated courses of steroid, or a constant dose to remain free of proteinuria and edema. It is interesting that not until the use of steroids in this disease did the frequently relapsing course become characteristic. Patients achieving remission without steroids generally remain well.

The use of frequently repeated or constant steroids leads to appreciable toxicity. The physical and psychological effects of Cushing's disease are reproduced. Lowered resistance to infection and longer term difficulties including cataracts and avascular necrosis of bone are seen.

These problems led to a search for alternative therapies, and immunosuppressive drugs (particularly the alkylating agents nitrogen mustard, cyclophosphamide and chlorambucil) were found to be effective in prolonging remission (4, 5). These drugs brought their own dangers however, including susceptibility to infection, to malignancies, hemorrhagic cystitis and sterility.

In fact, in 10 reported series of adult minimal change disease summarized in 1981 (6), including 232 patients followed for an average of 48 months (7–15), only 2 patients had developed renal failure while 21 deaths occurred. Most of the deaths were seen in resistant or relapsing patients who had been given large doses of steroids and other immunosuppressive drugs. Was there a net benefit from the use of these powerful and dangerous drugs in this population? The answer would be determined by an answer to these conflicting hypotheses:

a. Proteinuria is harmful to the kidney. Minimizing proteinuria with steroids or any other treatment could prevent progression to renal failure. These treatments may also cure the disease.
b. Proteinuria is not harmful to the kidney. Reducing proteinuria is only useful for controlling edema and other manifestations of the disease. The disease is self limited and does not progress to renal failure. Treatment only suppresses its signs and symptoms.

If a. were true then the morbidity due to treatment might well be an acceptable alternative to progressive renal failure in a large proportion

of patients. If b. were true, then such dangerous treatment would be unjustified.

It is difficult to distinguish between these possibilities. There is probably no practical mechanism for reducing proteinuria that does not also affect an underlying disease mechanism. For example, both protein restriction and prostaglandin inhibitor drugs may reduce proteinuria, but both are also likely to reduce renal blood flow and glomerular capillary pressure.

The surest way to compare the risks and benefits of prednisone (or other immunosuppressive) therapy would be through a prospective, randomized clinical trial. Unfortunately, large numbers of patients may be required, especially to detect a small benefit or establish that no substantial benefit results from treatment. Two such trials have been attempted.

In the prospective trial conducted by the British MRC (8) under the direction of Professor D.A.K. Black, 31 patients were randomly assigned to placebo or to prednisone. The prednisone dose was not standardized, but most patients received an average of about 25 mg/d for six months and then a slow taper thereafter. (Five patients in the control group were later given prednisone for "unsatisfactory progress"). Proteinuria remitted more rapidly in treated patients than in controls. After 2 years there was no longer any statistically significant difference between the groups. Four deaths occurred, all in the treated group and were considered possibly related to steroid effects. No renal failure occurred during the period of observation.

A second attempt was made by the United States based Collaborative Study of Adult Glomerular Disease as part of a larger series including other types of glomerular histology.

Adult patients with idiopathic nephrotic syndrome of minimal change type were randomly allocated to prednisone and placebo groups. Treatment consisted on average of 125 mg prednisone given in alternate-day doses for a period of 2 months. Relapses were re-treated.

When patients reached "stop points" (including a doubling of admission creatinine, severe steroid toxicity and certain other bad outcomes) they were removed from the constraints of the study but follow-up continued.

Twenty-eight patients were enrolled, with average age 30 and initial

TABLE 1
*Minimal Change—Population*

| | n | Age | Initial Proteinuria | Disease Duration | Follow-up "Blind" | Follow-up Total |
|---|---|---|---|---|---|---|
| Prednisone | 14 | 29 yr | 9.8 g/d | 2 mo | 60 mo | 69 mo |
| Control | 14 | 32 yr | 9.8 g/d | 2 mo | 50 mo | 85 mo |

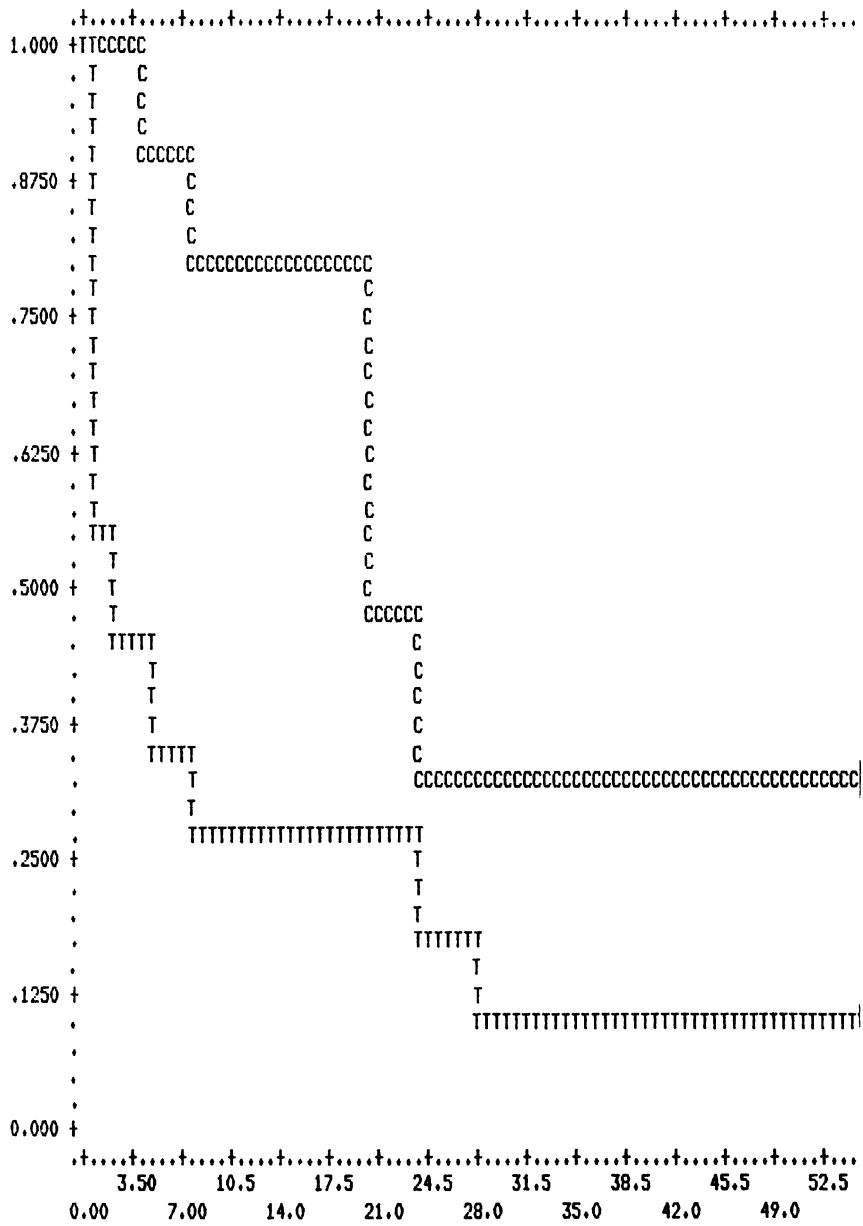


FIG 1. The proportion of study patients continuing to have 1 g or more proteinuria during follow-up. Months of follow-up are indicated on the horizontal axis. T = patients who received prednisone treatment. C = those who received placebo.

TABLE 2
*Minimal Change—Complete Remission*

| | Before Stop Point | Eventually |
|---|---|---|
| Prednisone | 12 | 13 |
| Control | 6 | 9 |

TABLE 3
*Minimal Change—Stop Points*

| | Doubled Creatinine | Total | |
|---|---|---|---|
| Prednisone | 0 | 4 | Steroid toxicity with repeated courses; psychosis avascular necrosis |
| Control | 4 | 5 | 1 "stress" |

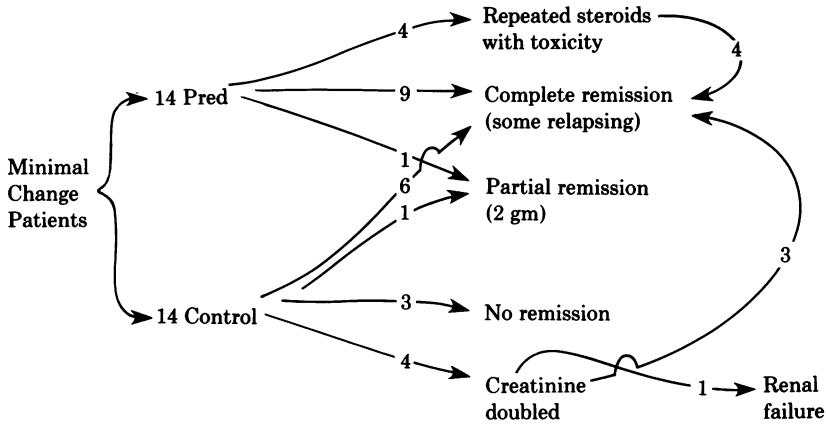


FIG 2. Outcomes in the treated and control patients. (See text).

urinary protein 9.8 g/d (Table 1). Median duration of symptoms at the time of entry was 2 months. Follow up before stop points averaged 55 months and total follow up 77 months. The patients treated with prednisone reduced their proteinuria significantly more rapidly than did those receiving placebo (Figure 1) with much of the drop occurring immediately during the treatment phase. Within a few months, however, proteinuria was also seen to fall in the control group. By 24 months there was no appreciable difference in the fraction of patients in the two groups with proteinuria below 1 g/d. Thirteen of 14 treated patients and 9 of 14 controls achieved complete remissions during the follow-up period (Table 2).

TABLE 4
*Minimal Change—Initial vs. Final*

| | Mean BP | Activity is Limited | Marked Edema |
|---|---|---|---|
| Prednisone | 96 → 95 | 2 → 1 | 12 → 0 |
| Control | 96 → 97 | 5 → 1 | 11 → 2 |

Of the control patients four doubled their serum creatinine values. Three of these occurrences were in the first 2 months of follow-up. These patients were withdrawn from the placebo and treated with steroids. All achieved complete remissions. The fourth progressed without a remission over the course of 2 years to renal failure and was transplanted 4 years after onset. One additional patient developed anxiety about his unknown medication and dropped from the study (Table 3).

Of the treated patients, four developed steroid toxicity from repeated courses of therapy (given for repeated relapses) including one patient with psychosis and one with avascular necrosis of both hips and one shoulder. A summary of these outcomes (within the period of observation) is presented in Figure 2.

No difference is apparent between the two groups with regard to blood pressure, edema or limitation of activity at the end of follow-up (Table 4).

With the exception of the single patient progressing directly to renal failure there was no difference in mean serum creatinine at the end of the study, or in the slope of 1/creatinine over time for the two groups.

## CONCLUSION

It is clear from both controlled studies reviewed here that prednisone results in a more rapid reduction of proteinuria than occurs in controls. Although all four deaths in the British study occurred in treated patients and the sole occurrence of chronic renal failure was seen in a control patient in our study, no significant difference in long-term outcomes was apparent.

This is, of course not equivalent to saying that no important differences could exist between treated and control groups. If, in fact, there were no important differences in outcome between groups, a study with a large number of patients followed for a long time would be needed to demonstrate that fact with confidence. I am quite sure that such a study will never be done.

The lesson for us, as we practice, may be clearer. If a short course of corticosteroids is effective in eliminating proteinuria, it will surely be worthwhile. If prolonged or repeated courses are necessary, or if immu-

nosuppressive agents are added to the regimen, the hazards of the treatment (including death) may exceed its benefit, and the physician should consider managing the symptoms of the nephrotic syndrome with diet, diuretics and other conservative measures.

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## DISCUSSION

**Futcher** (Philadelphia): What are the theories on the etiology of minimal change disease?

**Coggins:** The pathogenesis seems to reflect a loss of a dense layer of negatively charged substances in the glomerular capillary basement membrane. These negative charges normally repel albumin and other proteins that are negatively charged in the circulation and hence prevent their filtration. In minimal change nephrotic syndrome this charge structure is disrupted and the same proteins pass through the membrane. The cause of this charge

alteration is not so well understood. It may be that abnormalities of some sub-class of lymphocytes or of their humoral products may be involved.

**Chalmers** (New York): 30 years ago in 1955, Dr. Robert Morrison who had just finished a Fellowship with the late Dr. John Merrill, joined me at the Lemuel Shattuck Hospital, bringing with him the histories of about 100 adults with the nephrotic syndrome. If I remember rightly about 25% had the minimal change disorder. They were treated on the Metabolic Ward with steroids and wonderful observations were made on their response, and I pleaded on repeated occasions to begin a randomized control trial to determine the long term outcome; I was told that this would be unethical and it would be unfair to deprive the patients of their treatment. As you can see this morning I guess at least two trials have now been performed. If from the very early onset of the idea that both steroids and the immunosuppressive drugs might work, all patients had been entered into cooperative randomized control trials, we would have not 28 patients to look at but hundreds. The problem of small numbers would be solved by an adequate study. I cite this because it's typical of what has happened for the last 30–50 years, and we learn very slowly.

**Coggins:** The number of nephrotic patients with minimal change histology referred to our study was smaller than would have been expected from the frequency of that diagnosis in the general nephrotic population. Physicians apparently hesitate to refer that type specifically.

**Schreiner** (Washington): First, I would like to ask an historical question of you; whether you think attention to the potential immunologic basis for this disease came from the first use of steroids or whether it came from the use of nitrogen mustard by Chasis and Goldring at Bellevue when there were literally scores of patients with nephrotic syndrome who were occupying hospital beds for months and months on end. Another comment—I wish I could share Dr. Chalmer's panacea of the control trial as solving all scientific problems. The thing is that the perfect control trial is something that takes place with multiple equally skilled physicians and a presumed homogeneous disease. Unfortunately, even if we were to enter into that great millennium when we could control multiple physicians, we do not control the homogeneity of the disease. And I would like to point out that at least 3 trials have been done, including one at the NIH, when the failures were ultimately re-biopsied—and I did the biopsies. They did not have minimal change disease to start with, although they were put in with the control trial with a great deal of clinical assurance. So I don't believe that you can exclude focal sclerosis on a single biopsy. You point out in your own slide that one of the failures was found out to have focal sclerosis. No one can collect hundreds of cases and be absolutely sure that he has excluded focal sclerosis no matter how conscientious he is or how converted he is to the Chalmers hypothesis that we have to do a control trial. Unfortunately, Tom doesn't control the disease and the disease cannot be diagnosed with 100% certitude by a negative finding. That's the first point. The second point is that we have definitions by protocol which are not necessarily the definitions of reality. We say that something is frequently relapsing if the patients cannot stay protein-free without steroids for X period of time—you can choose what you want, 2-3-6 months (we happened to choose 6 months and at least twice around in our own study) but all that tells you is that either you're defining a different subset of a disease or you're dealing with some patients who are intermittently in contact with the antigen which caused their disease in the first place. So what you do to the patient who is out of contact with his allergen or the antigen responsible for inducing a flareup of his Nephrotic Syndrome is not going to have the same effect as what you do to the patient who remains in contact. Now, how do we know this? Because in Washington we have a control series which is called the State Department and the patients will frequently go overseas for five or six years. And I have a number of patients who were in our original series—well selected, conscientious, by us—as frequently relapsing steroid-dependent, steroid-responsive nephrotic syndromes, who got

their overseas assignments and lived in Greece or somewhere for six years without ever having a smidgeon of proteinuria. One returned to her house in Washington and had full-blown minimal change nephrotic syndrome within two weeks after return. So what you do therapeutically is going to depend on what is happening to the patient, whether or not he's getting repeated exposures or whether he's not getting a repeated exposure. So I think we have to be humble not just about the stupidity of doctors but also about the cantankerousness of the disease. Thank you.

**Coggins:** Dr. Schreiner's questions and comments would fuel hours of interesting conversation. Let me reply to two points: ACTH was tried first, and soon after both corticosteroids and nitrogen mustard were used with much activity around 1952–53. Dr. John Luetscher at Stanford and Dr. George Thorn at Harvard were among the leaders in these therapies.

Second, patients came to physicians participating in the Study about the way they come to any practicing doctor ... full of uncertainties! The more carefully the patients in the study are described as they progress through biopsy, treatment and follow-up, the more the practicing doc will know how the findings of the study relate to his individual patient.

**Langford** (Mississippi): I was going to ask you a question, but instead I want to respond to George Schreiner, too. Therapy demands adequate classification and prognosis. One of the first attempts at a controlled trial was that of Charles Pierre Eduarde Louis in the 1840s in France when there had been enough advance in the diagnosis and recognition of the progonosis of pneumonias and peripneumonias that one could look at the value of bleeding to treat these diseases. If we are in such a primitive state in the nephroses that we have no idea about prognosis and classification, then we can't do a clinical trial, Dr. Schreiner, and you may be correct; otherwise, we should.

**Barondess** (New York): I don't want to add to the turbidity of this discussion, but just to point out that the waters are made even murkier by efforts to pool data from multiple studies in the fashion that you indicated on the slide. It's very difficult to collect worthwhile retrospective data to begin with, but to pool data from multiple series presents difficulties suggested, I think, by one line on your slide in which most of the deaths came from a single study. Is that not the case?

**Coggins:** Most of the deaths came from two of the studies, which in turn had large numbers of patients. They were also studies in which the therapy may have been particularly vigorous and prolonged. Most of the studies were uncontrolled and the populations from which the patients were drawn were not adequately described. So I agree that it is very hard to guess what outcomes might have been given different therapy. The points to be made are that: 1. The incidence of death due to toxicity of therapy appeared to be high, and 2. The therapy reflects that used by experienced physicians in academic therapy.